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(54) Title: PYRIMIDINE NUCLEOTIDE PRECURSORS FOR TREATMENT OF SYSTEMIC INFLAMMATION AND INFLAMMATORY HEPATITIS

(57) Abstract

Pyrimidine nucleotide precursors including acyl derivatives of cytidine, uridine, and orotate, and uridine phosphorylase inhibitors, and their use in enhancing resistance to sepsis or systemic inflammation are disclosed.

Title of the Invention

PYRIMIDINE NUCLEOTIDE PRECURSORS FOR TREATMENT OF SYSTEMIC INFLAMMATION AND INFLAMMATORY HEPATITIS

Field of the Invention

This invention relates generally to pyrimidine nucleotide precursors including acyl derivatives of cytidine, uridine and orotate, and to the prophylactic and therapeutic uses of these compounds. The invention also relates to the administration of these compounds, alone or in combinations, with or without other agents, to animals. These compounds are capable of enhancing resistance of an animal to bacterial endotoxin and other inflammatory stimuli, and inflammatory mediators.

Background of the Invention

Sepsis, also referred to as sepsis syndrome, is a consequence of serious infection by bacteria, fungi, or viruses. Sepsis accounts for tens of thousands of deaths in

the United States every year; it is a leading cause of death of patients in surgical intensive care units.

Sepsis is an inflammatory disorder in which endogenous cytokines and other bioactive molecules, produced or released in response to an inflammatory stimulus such as bacterial endotoxin (a component of the cell wall of gram-negative bacteria), cause various symptoms including fever, neutropenia, blood coagulation disorders, hypotension, shock, and organ damage.

Sepsis (or in its more severe form, septic shock), is one example of a broader class of disease called the "Systemic Inflammatory Response Syndrome" (SIRS), which is an organism's reaction to inflammatory stimuli such as endotoxin (which can be present in the bloodstream without bacteremia, e.g. due to leakage of endotoxin from gram-negative bacteria into the circulation from a localized infection or from the intestine); SIRS can also be triggered by gram-positive bacteria, fungi, viruses, and can also be a consequence of autoimmune disorders or administration of therapeutic inflammatory cytokines.

Current treatment of SIRS involves circulatory and respiratory support, but does not directly address improvement of tissue resistance to inflammatory stimuli such as endotoxin, or inflammatory mediators.

Monoclonal antibodies for neutralizing endotoxins or mediators of its physiologic effects are under development. However, it is expensive or impractical to use antibodies as prophylaxis in susceptible patients, prior to the onset of

WHAT IS CLAIMED IS:

1. A method for treating or preventing tissue damage due to systemic inflammatory response syndrome comprising administering to an animal a therapeutically effective amount of a pyrimidine nucleotide precursor.

2. A method for treating or preventing sepsis comprising administering to an animal a therapeutically effective amount of a pyrimidine nucleotide precursor.

3. A method as in claim 2 wherein said pyrimidine nucleotide precursor is uridine, cytidine, orotic acid, or an acyl derivative of uridine, cytidine, or orotic acid, or a pharmaceutically acceptable salt thereof.

4. A method as in claim 3 wherein said acyl derivative of uridine is triacetyluridine.

5. A method as in claim 2 further comprising administering an inhibitor of uridine phosphorylase.

6. A method for treating or preventing sepsis comprising administering to an animal a therapeutically effective amount of an inhibitor of uridine phosphorylase.

7. A method for reducing toxicity of a therapeutic cytokine or inflammatory stimulus comprising administering to an animal a therapeutically effective amount of a pyrimidine nucleotide precursor prior to, during, or after administration of said cytokine or said stimulus.

8. A method as in claim 7 wherein said pyrimidine nucleotide precursor is uridine, cytidine, orotic acid, or an acyl derivative of uridine, cytidine, or orotic acid, or a pharmaceutically acceptable salt thereof.

9. A method as in claim 8 wherein said acyl derivative of uridine is triacetyluridine.

10. A method as in claim 7 wherein said cytokine or said stimulus is selected from the group consisting of interleukin 1, interleukin-2, interleukin 6, tumor necrosis factor, endotoxin, fungal polysaccharides, and double-stranded RNA.

11. A method as in claim 7 further comprising the step of administering an inhibitor of uridine phosphorylase.

12. A method for reducing toxicity of a therapeutic cytokine or inflammatory stimulus comprising administering to an animal a therapeutically effective amount of an inhibitor of uridine phosphorylase prior to, during, or after administering said cytokine or said stimulus.

13. A method as in claim 12 wherein said cytokine or said stimulus is selected from the group consisting of interleukin 1, interleukin-2, interleukin 6, tumor necrosis factor, endotoxin, fungal polysaccharides, and double-stranded RNA.

14. A method for treating cancer comprising administering to an animal a therapeutically effective amount

of a therapeutic cytokine or inflammatory stimulus and a therapeutically effective amount of a pyrimidine nucleotide precursor prior to, during, or after administration of said cytokine or said stimulus.

15. A method as in claim 14 wherein said pyrimidine nucleotide precursor is uridine, cytidine, orotic acid, or an acyl derivative of uridine, cytidine, or orotic acid, or a pharmaceutically acceptable salt thereof.

16. A method as in claim 15 wherein said acyl derivative of uridine is triacetyluridine.

17. A method as in claim 14 wherein said cytokine or said stimulus is selected from the group consisting of interleukin 1, interleukin-2, interleukin 6, tumor necrosis factor, endotoxin, fungal polysaccharides, and double-stranded RNA.

18. A method as in claim 14 further comprising the step of administering an inhibitor of uridine phosphorylase.

19. A method for treating cancer comprising administering to an animal a therapeutically effective amount of a therapeutic cytokine or inflammatory stimulus and a therapeutically effective amount of an inhibitor of uridine phosphorylase prior to, during, or after administering said cytokine or said stimulus.

20. A method as in claim 19 wherein said cytokine or said stimulus is selected from the group

consisting of interleukin 1, interleukin-2, interleukin 6, tumor necrosis factor, endotoxin, fungal polysaccharides, and double-stranded RNA.

21. A method for treating or preventing inflammatory hepatitis comprising administering to an animal a therapeutically effective amount of an acyl derivative of uridine, cytidine or orotic acid, or a pharmaceutically acceptable salt thereof.

22. A method as in claim 21 wherein said inflammatory hepatitis is due to viral infection.

23. A method as in claim 21 wherein said inflammatory hepatitis is due to autoimmune processes.

24. A method as in claim 21 wherein said inflammatory hepatitis is due to alcohol consumption.

25. A method as in claim 21 wherein said acyl derivative of uridine is triacetyluridine.

26. A method as in claim 21 including the further step of administering an inhibitor of uridine phosphorylase.

27. A method for treating or preventing inflammatory hepatitis comprising administering to an animal a therapeutically effective amount of an inhibitor of uridine phosphorylase.

28. A method for treating or preventing inflammatory hepatitis comprising administering to an animal a therapeutically effective amount of uridine or cytidine.

29. A method as in claim 28 wherein from 2 to 40 grams of uridine or cytidine are administered per day.

30. A method for treating or preventing hepatic damage in an animal receiving parenteral nutrition comprising administering intravenously to said animal a therapeutically effective amount of a pyrimidine nucleotide precursor.

31. A method as in claim 30 wherein said hepatic damage is due to said animal receiving parenteral nutrition.

32. A method as in claim 30 wherein said pyrimidine nucleotide precursor is uridine, cytidine, orotic acid, or an acyl derivative of uridine, cytidine, or orotic acid, or a pharmaceutically acceptable salt thereof.

33. A method as in claim 30 wherein from 2 to 40 grams of said pyrimidine nucleotide precursor are administered per day.

34. A method as in claim 30 including the further step of administering an inhibitor of uridine phosphorylase.

35. A method for treating or preventing hepatic damage in an animal receiving total parenteral nutrition comprising administering to said animal an inhibitor of uridine phosphorylase.

36. A method for treating or preventing hepatic damage in an animal receiving a liver transplant comprising administering to said animal a therapeutically effective amount of a pyrimidine nucleotide precursor.

37. A method as in claim 36 wherein said pyrimidine nucleotide precursor is uridine, cytidine, orotic acid, or an acyl derivative of uridine, cytidine, or orotic acid, or a pharmaceutically acceptable salt thereof.

38. A method as in claim 36 wherein from 2 to 40 grams of said pyrimidine nucleotide precursor are administered per day.

39. A method as in claim 36 including the further step of administering an inhibitor of uridine phosphorylase.

40. A method for treating or preventing hepatic damage in an animal receiving a liver transplant comprising administering to said animal an inhibitor of uridine phosphorylase.

41. A composition comprising:

a) an acyl derivative of a pyrimidine nucleotide precursor

and;

b) an inhibitor of uridine phosphorylase

42. A composition comprising:

a) an acyl derivative of a pyrimidine nucleotide precursor

and;

b) a purine nucleotide precursor.

43. A composition as in claim 42 where said pyrimidine nucleotide precursor is uridine, cytidine, or orotate.

44. A composition as in claim 42 where said purine nucleotide precursor is inosine, adenosine, or an acyl derivative of inosine or adenosine.

45. A composition comprising a parenteral nutrition formula and 2 to 40 grams of a pyrimidine nucleotide precursor per daily portion

46. A composition as in claim 45 wherein said pyrimidine nucleotide precursor is uridine, cytidine, orotic acid, or an acyl derivative of uridine, cytidine, or orotic acid, or a pharmaceutically acceptable salt thereof.

47. A method of providing nutrition to a mammal receiving nutrition intravenously comprising administering to said mammal the composition of claim 45.

48. A composition comprising

a) glucose, and

b) a pyrimidine nucleotide precursor.

49. A composition as in claim 48 wherein said composition is an aqueous solution containing 1 to 10 % glucose.

50. A composition as in claim 48 wherein said composition is an aqueous solution containing 5 % glucose.

51. A composition as in claim 48 wherein said pyrimidine nucleotide precursor is uridine or cytidine.

52. A method of treating a mammal during or after liver transplantation comprising administering the composition of claim 48.

53. A method for reducing the effects of ethanol intoxication comprising administering to a mammal in need of such treatment uridine, cytidine, orotic acid, or an acyl derivative of uridine, cytidine, or orotic acid, or a pharmaceutically acceptable salt thereof.

54. A method of treating ethanol intoxication comprising administering to an intoxicated mammal uridine, cytidine, orotic acid, or an acyl derivative of uridine, cytidine, or orotic acid, or a pharmaceutically acceptable salt thereof.

55. A method as in claim 54 wherein said administering step comprises administering triacetyluridine.

56. A method as in claim 54 wherein said administering step comprises administering uridine or cytidine.

57. A method of reducing inflammatory liver injury in an animal in need of such treatment comprising administering to said animal a therapeutically effective amount of an acyl derivative of uridine, cytidine or orotic acid, or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US95/08259

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 31/70; C07H 19/067, 19/167
US CL :U.S.: 514/45,46,49,50,256; 424/85.1, 85.2, 85.4, 85.5
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : U.S.: 514/45,46,49,50,256; 424/85.1, 85.2, 85.4 and 85.5

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

None

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X ---- Y	WO, A, 94/13687 (PRO-NEURON INC.) 23 JUNE 1994, see claims 1 - 41.	1 - 21, 25 - 30, 32 - 44 ---------- 22 - 24, 31, 45 - 57
Y	WO, A, 89/03837 (PRO-NEURON, INC.) 05 MAY 1989, see especially claims 22 - 23.	1 - 57

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US95/08259

B. FIELDS SEARCHED
Electronic data bases consulted (Name of data base and where practicable terms used):

APS and CAS: acylated nucleosides; systemic inflammatory hepatitis, sepsis, cancer, liver transplants, nucleoside prodrug, cytokines, parenteral nutrition, alcohol intoxication